PATENT APPLICATION

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...Application _____ papers.

2. Request for Change

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PATENT APPLICATION SERIAL NO. _____

U.S. DEPARTMENT OF COMMERCE
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FEE RECORD SHEET

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PTO-1556
(5/87)

*U.S. GPO: 1998-433-214/80404

SERIAL NUMBER	FILING DATE	CLASS	GROUP ART UNIT	ATTORNEY DOCKET NO.
60/151,668 PROVISIONAL	08/31/99		0000	P-68392-1/DJ

APPLICANT

TODD DICKINSON, SAN DIEGO, CA.

CONTINUING DOMESTIC DATA********
VERIFIED

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371 (NAT'L STAGE) DATA********
VERIFIED

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FOREIGN APPLICATIONS********
VERIFIED

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IF REQUIRED, FOREIGN FILING LICENSE GRANTED 09/20/99

Foreign Priority claimed 35 USC 119 (a-d) conditions met Verified and Acknowledged	☐yes ☐no ☐yes ☐no ☐Met after Allowance Examiner's Initials _____ Initials	STATE OR COUNTRY	SHEETS DRAWING	TOTAL CLAIMS	INDEPENDENT CLAIMS
		CA	0		

ADDRESS

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TITLE

METHOD FOR IMPROVING SIGNAL DETECTION FROM MICROARRAYS

FILING FEE RECEIVED	FEES: Authority has been given in Paper No. _____ to charge/credit DEPOSIT ACCOUNT NO. _____ for the following:	☐ All Fees ☐ 1.16 Fees (Filing) ☐ 1.17 Fees (Processing Ext. of time) ☐ 1.18 Fees (Issue) ☐ Other _____ ☐ Credit
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PROVISIONAL APPLICATION COVER SHEET

This is a request for filing a PROVISIONAL APPLICATION under 37 CFR 1.53(c)

"EXPRESS MAIL" MAILING LABEL Number EL445337637US, Date of Deposit August 31, 1999

I hereby certify that this paper or fee and listed enclosures is being deposited with the United States Postal Service "Express Mail Post Office to Addressee" service under 37 C.F.R. 1.10 on the date indicated above and is addressed to Box Provisional Patent Application, Assistant Commissioner for Patents, Washington, D.C. 20231, on August 31, 1999.

Typed or Printed Name: Grady Domingo

Signed:

Docket Number:	P-68392-1/DJB/RMS	Type a plus sign (+) inside this box →	+

INVENTOR(s)/APPLICANT(s)

LAST NAME	FIRST NAME	MIDDLE INITIAL	RESIDENCE (CITY AND EITHER STATE OR FOREIGN COUNTRY)
DICKINSON	Todd		San Diego, California

TITLE OF THE INVENTION (280 characters max)

METHOD FOR IMPROVING SIGNAL DETECTION FROM MICROARRAYS

CORRESPONDENCE ADDRESS

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STATE	CA	ZIP CODE	94111	COUNTRY	US

ENCLOSED APPLICATION PARTS (check all that apply)

X	Specification	Number of Pages	6		Small Entity Statement
	Drawings	Number of Sheets			Other (specify):

METHOD OF PAYMENT OF FILING FEES FOR THIS PROVISIONAL APPLICATION FOR PATENT (check one)

X	A check (No. 25786) or money order is enclosed to cover the Provisional filing fees	PROVISIONAL FILING FEE AMOUNT $150.00	$150
	The Commissioner is hereby authorized to charge filing fees and credit Deposit Account Number: 06-1300 (OrderNo. P-68392-1/DJB/RMS)		

The invention was made by an agency of the United States Government or under a contract with an agency of the United States Government.

X No.

Yes, the name of the U.S. Government Agency and the Government contract number are: _____

Respectfully submitted,

SIGNATURE: Robin M. Silva Date August 31, 1999

TYPED or PRINTED NAME Robin M. Silva REGISTRATION NO. (If appropriate) 38,304

Additional inventors are being named on separately numbered sheets attached hereto.

USE ONLY FOR FILING A PROVISIONAL APPLICATION FOR PATENT

Burden Hour Statement: This form is estimated to take .2 hours to complete. Times will vary depending upon the needs of the individual case. Any comments on the amount of time you are required to complete this form should be sent to the Chief Information Officer, Assistant Commissioner for Patents, Washington, DC 20231. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SEND TO: Box Provisional Application, Assistant Commissioner for Patents, Washington, D.C. 20231.

INVENTION DISCLOSURE FORM

This form is provided to permit evaluation of the patent potential of company inventions, and to facilitate preparation of patent applications when warranted. Please fill in each space as completely as possible, and use additional sheets when necessary.

1. Name: Todd Dickinson

2. Date:

3. State the Title of the Invention: Method for Improving Signal Detection from Microarrays

4. Describe the invention: Use additional sheets if necessary. Attach descriptive materials such as drawings, sketches, photographs, etc. which may help illustrate the invention. Delineate new and important features. Make sure to include both the preferred embodiment as presently identified, and alternative constructions, procedures or equivalent components which can accomplish the same result as the preferred embodiment.

The ability for any analytical system, optical or otherwise, to detect a change in signal is dictated by the background and noise associated with that signal. Exploring different ways to improve the signal to background ratio by either amplifying the signal, reducing the background, or both, is thus a critical area of research during the development of any type of analytical detection system.

One of the primary sources of background in optical microarray systems is the intrinsic fluorescence of the array substrate. In the present Illumina array configuration, the fluorescence of microspheres immobilized at the distal tip of the imaging fiber bundle is imaged from the proximal end of the bundle. While this approach has a number of advantages, most importantly being the remote sensing capability and the ease of sample interface, the background of the measurement will necessarily include any fluorescence originating from the fiber core glass itself. Since each fiber element is its own waveguide, it is particularly susceptible to generating high fluorescence readings on the detector since the fluorescence of the glass constituents as well as any contaminants present at the core-clad interface will be captured and propagated down the fiber and measured by the detector. Conversely, if one turns the fiber around and images the bead array directly, the background is found to be slightly reduced (most likely due to the fact that the focal plane is no longer placed on the glass itself, but rather on the beads in the wells, and thus collection of core fluorescence is not as efficient). This effect is shown in Figure 1.

5. State the primary purpose of the invention, including the need satisfied or problem solved by the invention:

The purpose of the present invention is to enhance the optical signals that are collected from a microarray either through a unique method of increasing signal collection efficiency, reducing background, or a combination of both. There is a critical need for high sensitivity in the array field for a wide range of assays: for example, high sensitivity can lead to 1) improved accuracy of results, 2) a broader range of assays that can be performed, 3) higher throughput of assays and reduced costs due to less stringent requirements on sample concentration. The present invention may accomplish some of these results by improving the overall sensitivity (lowering the detection limit) of optical microarrays, and incresing the dynamic range of system, allowing quantitation over a larger concentration range.

6. Please list what you feel is the prior art: please include references, articles, talks, abstracts, patents, etc. which are relevant to either the state of the prior art or to the invention. Please include dates and provide copies whenever possible:

Diping Che has done some similar work with other devices – no publications have been made yet, but he has delivered two talks on the subject:

"A novel surface, attachment chemistry and CCD-based Imaging system for analysis of genomic DNA arrays" D. Che et. al., Journal of Scanning Microscopies, 21(2), 63-64, 1999.

"Microarray chip based on comparative genomic hybridization", D. Che, International Business Conference on *Massively parallel DNA analysis*, San Francisco, August, 1998.

7. Are there any publications, abstracts, submitted manuscripts, talks, etc. on this work (either already done or in the works)? Please provide details and dates:

None.

8. Compare new and important features of the invention with the prior art, explaining why and how the invention is better:

The present invention applies to patterned substrates, and to microsphere arrays.

9. Please list known competitors or alternate technologies which solve the same problem:

None known.

10. Are there commercial products you envision? Please describe:

This process could easily be incorporated into the manufacturing process of Illumina's Array of Arrays technology. It is likely that there are many other potential applications of this type of signal improvement in other types of optical analytical systems as well.

11. What are the immediate research plans or steps to be taken:

Repetition of experiments, and checking additional fluorescence channels for similar S/N improvements.

12. What are the longer term research plans or steps to be taken:

Other metal films, as well as varying thicknesses, should be explored. Metal coating adhesion to various polymer substrates should be investigated. Imaging systems capable of direct distal-end imaging need to be developed. Sample interface issues will need to be addressed.

13. Earliest date and place invention was conceived, and substance of conception (identify people and records to support date and place, such as notebook numbers and pages):

Invention was first recorded by Todd Dickinson on August 17, 1999, on page 156 of Illumina Lab Notebook 0004 (Todd Dickinson) – idea originally conceived in July, and discussed with Dr. Diping Che in early August.

It may be possible to achieve the same benefits that coatings offer without applying coatings at all: this would be possible if one were able to identify or fabricate a substrate material (plastic or otherwise) that is opaque and reflective itself. Opaque materials such as many black plastics are typically accompanied by low intrinsic fluorescence levels, in large part due to efficient light absorption by the bulk material. Additionally, it may be possible to render the surface of the substrate reflective by generating or treating it in such a way as to create a very smooth finish. If the process of forming the wells in the array (whether by etching, imprinting, stamping, ablating, or other method) causes the bottom of the well to become less reflective by, for example, roughening the surface, it may be necessary to treat the array in some manner, such as a gentle, partial melting process, to return the glossy finish to the substrate material.

As another method of improving signal collection from microarrays, one could design the well bottoms to be concave in shape, thus acting like individual micro-reflectors at the bottom of each well (Figure 1). This would serve two purposes: 1) re-directing stray excitation light back into the bead to generate additional fluorescence, and 2) reflecting fluorescence emission from the bead back into the collection optics for improved signal collection. This is similar to the concept employed in traditional arc lamps, where lamp output is enhanced significantly by placing a concave reflector directly behind the arc.

Figure 1.

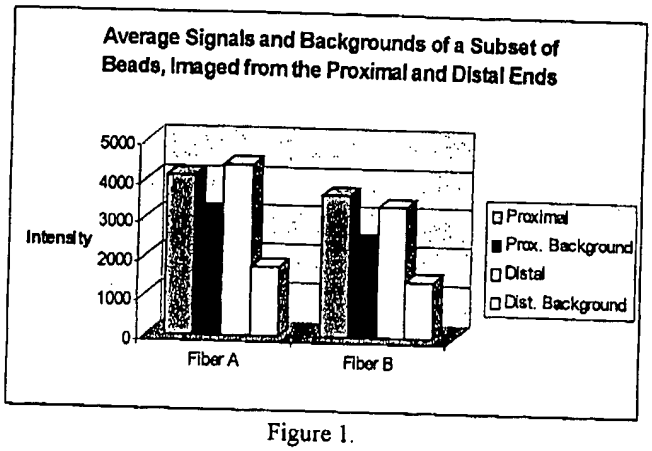


Figure 1.

In this configuration, where one no longer needs to view through the fiber, one could imagine placing a non-fluorescent coating such as a thin metal film over the etched array that blocks the excitation light from hitting the fluorescent substrate underneath, thereby effectively reducing the background of the array. Preliminary experiments indicate that this is indeed possible (Figure 2).

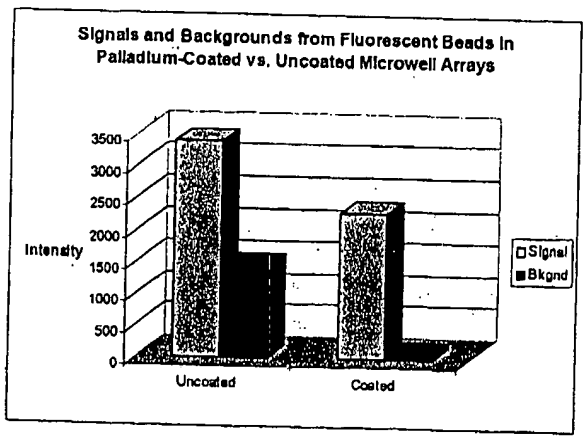
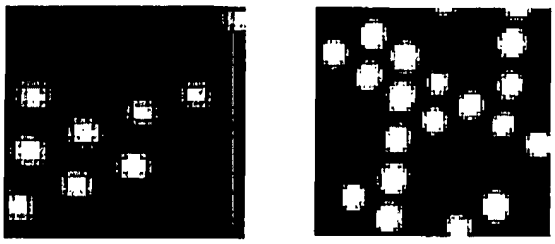


Figure 2a)



b) c)

Figure 2. a) A comparison of signals and backgrounds from a single bead type (fluorescein-labelled silica) assembled in a Pd-coated vs. uncoated etched fiber array. Fluorescence image of beads in b) uncoated etched fiber (signal to background of 2.47), and c) Pd-coated etched fiber (signal to background of 28.78).

For this experiment, fluorescein-labelled silica beads were loaded into two different etched fiber bundles: one coated with a thin palladium film (via vapor-deposition), the other uncoated. The average intensities of a subset of beads and empty cores were measured for each fiber and graphed in Figure 2a. The results indicate a substantial reduction in background of the metal-coated fiber as compared to the uncoated fiber, resulting in a 10-fold improvement of the signal-to-background ratio.

These experiments indicate that a) metal films can provide a non-fluorescent, low-background coating for array substrates that improves signal-to-background ratios, and that b) the film does not prevent the immobilization of microspheres into microwell arrays. Furthermore, it is possible that similar metal or other types of coatings could be applied to other substrate materials such as plastics (e.g. polycarbonate, polyamide, polymethyl methacrylate, polysulfone, etc.), silicon, silicones, quartz, and other materials. It is important to note that the ability to lay down a non-fluorescent coating over a patterned substrate material obviates the need to use materials with intrinsically low fluorescence, thus broadening the scope of materials available for generating array platforms.

An added benefit to coating a microarray substrate material may be more efficient signal collection through reflection. Provided an appropriate metal coating is chosen, it is likely that we can harness more of the fluorescence emitted from each bead by creating a reflective surface which can direct fluorescence back toward the detector. There are a wide array of coatings that could prove useful for this application, such as gold, silver, chromium, platinum, and indium tin oxide.

This technique could be used to improve sensitivity of a wide range of assays, including SNP genotyping, small molecule screening, immunoassays, enzymatic assays, and any other chemical or biological assay that can be performed in an optical microarray format.

PTO/SB/31 (7-03)
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REQUEST FOR ACCESS TO AN ABANDONED APPLICATION UNDER 37 CFR 1.14

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FEB 24 2004
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In re Application of

Application Number	Filed
60/151,668	6,30,00

Paper No. #2

I hereby request access under 37 CFR 1.14(a)(1)(iv) to the application file record of the above-identified ABANDONED application, which is identified in, or to which a benefit is claimed, in the following document (as shown in the attachment):

United States Patent Application Publication No. 0001/18524 page, _____, line _____.

United States Patent Number _____, column _____, line, _____, or

WIPO Pub. No. _____, page _____, line _____.

Related Information about Access to Pending Applications (37 CFR 1.14):

Direct access to pending applications is not available to the public but copies may be available and may be purchased from the Office of Public Records upon payment of the appropriate fee (37 CFR 1.19(b)), as follows:

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Kelvin Rodriguez
Signature

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Kelvin Rodriguez
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In re Application of

Application Number	Filed
60/157668	Aug 31, 1999

Paper No. #3

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United States Patent Application Publication No. _____, page, _____ line _____.

United States Patent Number 6942958, column _____, line, _____ or

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(2) If the application is incorporated by reference or otherwise identified in a U.S. patent, a statutory invention registration, a U.S. patent application publication, or an international patent application publication in accordance with PCT Article 21(2), a member of the public may obtain a copy of:
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